[Review]

Potential Role and Challenges of Methadone in Cancer Pain Management

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Abstract: While remarkable progress has been made in strategies for cancer treatment, strategies for cancer pain management are still in their infancy with respect to translating results from animal models to the clinical setting, due to the complex biopsychosocial nature of cancer pain. Although conventional cancer pain management based on the World Health Organization three-step ladder may serve well for the majority of patients, up to 30% of patients with cancer pain may not benefit from the standard approach. The strategy of switching from one opioid analgesic to another, in order to overcome worsening side effects while attempting to improve analgesic efficacy, has been empirically accepted. This practice has been strongly based on the assumed equianalgesic dose ratio between opioids. However, the growing realization of opioid-induced hyperalgesia and the role of methadone in receptor recycling have provided new insights into the mechanism of cancer pain that does not respond to conventional opioid treatment. As cancer is no longer considered a terminal disease, concern has been raised about the side effects of long-term opioid therapy. Although methadone has been recognized as pharmacokinetically challenging to use, its unique pharmacodynamic properties may provide advantages over other opioid analgesics. Establishing phenotypes that respond to certain types of approach may help clinicians to stratify the approach further.

Key words: methadone, cancer pain, tolerance, opioid-induced hyperalgesia, opioid switch (rotation, substitution)

INTRODUCTION

Opioid analgesia and cancer pain: revealing the reality

To date, opioid analgesics and adjuvant analgesics have been considered the gold standard for cancer pain management. The traditional mainstay of pain management since the 1980s has been the World Health Organization (WHO) three-step "ladder" approach, which recommends a strong opioid for moderate to severe cancer pain.

However, a recent systematic review of randomized trials of opioid analgesics for cancer pain raised the concern of significant limitations in the availability of evidence to support clinical practice. The difficulty in performing and justifying randomized trials with sufficient sample size in cancer settings, especially for long-term follow up beyond 4 weeks, was noted. The lack of uniform measures of pain, as well as variability in the definition of statistically significant pain relief, was also addressed.[1] A recent population-based, retrospective cohort study in primary care in the United Kingdom revealed that prescribing behavior, rather than patient factors, plays an important role in multiple opioid prescribing at the end of life; this highlights the need for training and education for clinical practitioners that goes beyond the well-recognized WHO approach.[2]

The lack of evidence for efficacy and safety of long-term opioid therapy may present further challenges in modern cancer pain management, as cancer is no longer considered a terminal disease. Some data suggests that 50–65% of patients with cancer survive for at least 2 years, while a number of patients with cancer survive for much longer or are cured. A national prescription database study in Norway revealed a trend for an increasing proportion of cancer patients surviving for 12 months after methadone was prescribed. In this longitudinal pharmacoepidemiological study, 22.7% and 62.7% of patients were alive at 12 months after prescription of methadone in 2005 and 2009, respectively.[3] There is increasing concern about the side effects of long-term opioid therapy, such as issues with the endocrine system, tolerance, abuse, and addiction, for patients with not only non-cancer pain syndromes but also cancer pain.

Clinical observations revealed that 10–30% of cancer patients treated with oral morphine could not reach a balance between sufficient pain control and an acceptable level of side effects.[4] A Cochrane review on opioid switching concluded that a switch to an alternative opioid might be the only option for symptomatic relief in some patients with cancer pain. However, there is a lack of randomized controlled trials to establish the true effectiveness of this clinical practice, to determine which opioid should be used first or second-line, and to stan-

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dardize conversion ratios when switching from one opioid to another. In the 52 reports including both cancer and chronic non-cancer pain populations, morphine was used most frequently as a first-line opioid and methadone was used as a second-line opioid.[5]

Most reports of switching to methadone for refractory pain or adverse effects with other opioids have been favorable. Initial reports of switching to methadone in cancer patients found a dramatic dose reduction as well as frequent improvement in pain intensity and opioid toxicity.[6] However, in a systematic review to determine effectiveness and safety of methadone analgesia in cancer patients, including nine RCTs (six double blinded, two crossover) with 459 recruits and 392 completing patients, efficacy and tolerability were broadly similar between methadone and morphine, although no meta-analysis was possible due to various methodologies without consistent reporting of pain data.[7]

Data from a nation-wide longitudinal pharmacoepidemiological study from the national drug prescription database in Norway between 2004 though 2009 revealed that a total of 292 patients were switched from another opioid to methadone. Of these, 168 (58%) were patients with cancer, and the remainder were patients with chronic non-cancer pain. One hundred and thirty (77%) out of 168 cancer patients received more than one dispensed prescription of methadone. Of 168 cancer patients, 48 (29%) had tried two strong opioids prior to the switch to methadone, whereas 21 (12.5%) had tried three or more strong opioids. The authors concluded that opioid switching to methadone appears to provide a long-lasting improvement in pain control in a significant proportion of patients. However, the study raises concern that treatment options with less risk are not being exhausted prior to switching to methadone.[3]

In this article, the unique pharmacokinetic and pharmacodynamic characteristics of methadone will be extensively reviewed. Furthermore, the current clinical evidence on opioid switching (i.e. opioid rotation or substitution) to methadone as one of the powerful strategies to overcome significant limitations of opioid analgesics will be reviewed. Finally, the role of methadone in cancer pain management based on the available evidence will be extensively discussed.

METHODS

All major relevant research on methadone was identified through PubMed and MEDLINE using the search terms "methadone" and "cancer pain management." Further references were handsearched to supplement evidence beyond cancer pain, due to limited availability of evidence. As a result, this review is narrative in scope.

RESULTS

Basic pharmacokinetics of methadone compared with morphine

Methadone presents advantages in several pharmacodynamic characteristics over other μ-opioid receptor agonists. However, its pharmacokinetic characteristics are potentially disadvantageous unless clinicians are well equipped to manage them. Characteristics include high bioavailability, very long serum elimination half-life, potential for drug-drug interactions with concurrent pharmacotherapies and risk of Torsades de pointes arrhythmia. Therefore, it is necessary for clinicians to be familiar with the basic pharmacokinetics of methadone when considering prescribing.

The pharmacokinetics of morphine and methadone differ in several ways. The reported oral bioavailability of single administration of morphine is 25–35%,[8, 9] with a range of 10% to 43%.[10] The oral bioavailability of methadone is usually 70–90%, with a range of 40% to 99%,[10–12] which is far higher than other opioids. Although methadone has high lipid solubility, with 98% of drug reaching the central compartment and only1–2% remaining in the blood compartment at steady state, the volume of distribution is comparable to other opioids due to its high protein binding capacity of 85–90%, primarily to α-glycoprotein.[13–15] While plasma elimination half-life for morphine is 2–3 h,[10, 16] methadone has a rapid and extensive initial distribution phase within 2–3 h, and a prolonged elimination phase lasting for 15–60 h,[10] and sometimes as high as 120 h,[17] whereas the duration of analgesia is often only 4 to 8 h.[18] These pharmacokinetic parameters explain the variability in time for methadone to reach steady state, ranging from 35 to 325 h (13.5 days).[19] In other words, in a patient for whom the methadone half-life is 60 h, it would take almost 12 days on a stable dose of methadone to approach a steady state (5 half-lives). Clinicians should be aware that the variable half-life of methadone means that some patients may not reach steady state (5 half-lives) for over 3 weeks.

Methadone is primarily excreted via the fecal route and very little methadone appears in the urine. Although a proportion (20% of unchanged drug) is excreted in the urine, neither the parent drug nor its metabolites seem to be dependent on the kidney for elimination. Due to the highly individual and long serum elimination half-life with high volume of distribution, as well as potential for drug-drug interactions, caution is required; yet, methadone may be an option in cases with renal failure.[20]

Drug-drug interactions

In clinical settings where multiple pharmacotherapies are involved, use of methadone is extremely challenging in relation to drug-drug interactions. Experimental studies have indicated that methadone and several other opioids are P-glycoprotein/multi drug resistance protein 1 (MDR1) substrates.[21] P-glycoprotein acts as an efflux pump in several tissues, including the capillary endothelium in the blood brain barrier and the intestinal epithelium.[22] Its function is to actively transport substrate drugs out of the brain, thereby limiting brain access, and decreasing pharmacological effects. In healthy volunteers administered methadone orally, inhibition of P-glycoprotein with quinidine resulted in a significant increase of plasma methadone concentrations and a 1/3 decrease in

T_{max}, while C_{max} and area under the curve (AUC) were unchanged, suggesting that intestinal P-glycoprotein increased oral methadone absorption. However quinidine did not affect intravenously administered methadone pharmacodynamics, suggesting that P-glycoprotein did not appear to be a determinant of the access of methadone to brain.[23] Other P-glycoprotein inhibitors often encountered in cancer care include doxorubicin, vinblastine, and actinomycin.

Methadone's metabolism in humans is complex. Methadone is metabolized by human intestinal and hepatic microsomes with 20–30% of administered dose undergoing first pass extraction. The primary route of metabolism and inactivation is N-demethylation to EMDP (2-ethyl-5-methyl-3, 3-diphenylpyrroline), and then to EDDP (2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrroline), catalyzed predominantly by CYP 3A4 isoenzyme, one of many isoforms of the hepatic cytochrome P450 enzyme system in intestine and liver. Other metabolites are produced via other pathways, but appear to play a minor role. To date, none of the methadone metabolites have been shown to be active. The CYP 1A2 and 2D6 isoenzymes also appear to be involved in methadone metabolism. Methadone appears to strongly inhibit the CYP 2D6 isoenzyme. Chronic administration of methadone along with a drug that is a CYP 2D6 substrate may, therefore, increase the other drug's effects. It is postulated that the CYP 2B6,[24] CYP 2C9 and CYP 2C19 isoenzymes also may be involved, but to a much lesser degree.

A multitude of drugs, many of them frequently used in the palliative care setting, may either inhibit or induce the enzymes that metabolize methadone and other opioids. When these enzymes are inhibited, the effects of the opioids may be increased, and when they are induced, the analgesic potency of the drugs may be compromised.[25] Inhibitors of the CYP 3A4 isoenzyme include ciprofloxacin, clarithromycin, erythromycin, norfloxacin, fluoxetine, fluvoxamine, sertraline, nefazadone, cimetidine, fluconazole, itraconazole, and ketoconazole. Inducers include nevirapine and ritonavir (part of HIV maintenance therapy), carbamazepine, phenytoin, phenobarbital and cocaine. Patients who take inducers (medications that promote methadone metabolism or inhibit its effects) should avoid abrupt cessation of such medications.

_N_-Methyl-D-aspartate (NMDA) antagonism and receptor recycling

One of the most significant pharmacodynamic characteristics of methadone is the role of the _N_-methyl-D-aspartate (NMDA) receptor. Methadone has an asymmetric carbon atom resulting in two enantiomeric forms, the _d_- and _l_-isomers. The racemic mixture (_dl_- methadone) is the form commonly used clinically and in laboratory studies. The _l_-isomer possesses analgesic activity through μ-opioid receptor, while the _d_-isomer is inactive or weak as an opioid.[26] Although both isomers bind to the non-competitive side of the _N_-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord synaptic membranes, _d_-methadone administered intrathecally has shown antinociceptive effect through NMDA receptor antagonism, but not through μ-opioid receptor. Furthermore, _d_-methadone was reported to have blocked the development of morphine tolerance after systematic or intrathecal administration.[26, 27]

Extensive data on the role of NMDA receptors and of their antagonists indicates NMDA receptor blockade as a mechanism for neuropathic pain antinociception. In the animal model, methadone inhibition of noxious evoked activity in normal rats is achieved predominantly through the μ-opioid receptor agonism, while inhibition of the pain-related hyperactivity in rats with signs of neuropathic pain also involves NMDA antagonism.[28] However, differences in the equianalgesic dose ratios of morphine to methadone in patients with or without neuropathic pain were not confirmed in a retrospective clinical data analysis.[29]

Clinical evidence shows that NMDA-receptor antagonists may induce analgesia in patients refractory to other μ-opioid agonists, and that tolerance develops more slowly with chronic infusion of methadone than of morphine.[30]

Another unique pharmacodynamic characteristic of methadone is found in receptor desensitization, arrestin (which by binding to the G-protein couple receptor, such as μ-opioid receptor, blocks further G-protein mediated signaling and targets receptors for internalization) recruitment, and endocytosis as the possible mediators for analgesic tolerance. Although morphine fails to drive significant endocytosis of the μ-opioid receptor, methadone is the only clinically used analgesic known to more closely mimic endogenous opiates and promote substantial endocytosis and recycling by promoting substantial arrestin recruitment. Chronic administration of moderate doses of methadone has been reported to produce significantly less analgesic tolerance than morphine.[31] To promote μ-receptor endocytosis and re-sensitization (recycling), methadone doses do not have to be in analgesic concentrations.[32]

Serum concentrations

A single dose of methadone taken orally is detectable in the plasma in 30 min after administration. There are considerable differences in the time needed to reach the maximum plasma concentration (T_{max}), on average 2.5–4.4 h with its plasma concentrations over time following a bi-exponential curve with a rapid α-phase (distribution), that corresponds to the transfer of the drug from the central compartment to the tissue compartment and to the beginning of elimination, and a slow β-phase, that corresponds to elimination. $T_{1/2}$ of the α-phase (disappearance from plasma) varies from 1.9–4.2 h, while $T_{1/2}$ of β-phase varies even more from 8.5–47 h. Also methadone body clearance varies widely among individuals.[13, 33] A study in chronic non-cancer pain patients observed stable serum concentrations of methadone and EDDP during 9 months of treatment with stable doses.[3] This finding contradicts the hypothesis of metabolic tolerance and autoinduction of hepatic enzymes during long-term

methadone therapy.[34]

Although review articles have cited fatal methadone plasma concentrations ranging from 60 to 450 mg/ml, blood levels found in patients who died of methadone overdose sometimes are the same as blood levels that are therapeutic for other individuals.[35] Measurement of serum concentrations of the parent compound and its metabolites may identify patients who differ significantly from the rest, and thus contribute to the understanding of inter-individual variations in opioid pharmacology. However, measuring serum concentrations have little contribution to pain management planning for clinicians unless screening for adherence to the analgesic regimen.

Clinical evidence of opioid switching involving methadone

Clinical evidence generally supports that methadone has a significant role in improving pain management and improving adverse effects when switching from other μ-opioid receptor agonists. However, in general, methadone has been considered as a second line μ-opioid analgesic after failing analgesic management with other opioids. A systematic review of 22 clinical trials and 19 case reports or series involving switching to methadone from other opioid analgesics (morphine, hydromorphone, and others) due to inadequate analgesia and/or adverse effects in a total 730 patients (625 patients or 88.9% with diagnosis of cancer) between 1966 and 2006 revealed a positive correlation between the previous morphine equivalent daily dose (MEDD) and MEDD/final methadone dose ratio.[36] Despite various methods of switching, 46–89% of rotations were successful.

Subsequently, similar results were reported through a retrospective analysis of 54 cancer inpatients requiring switching to methadone from morphine. In this study, multiple linear regression analysis showed that the reason for switching (pain versus side effects; $p = 0.001$) and previous morphine doses (< 300 mg/day versus ≥ 300 mg/day; $p < 0.001$) were independently associated with MEDD/final methadone dose ratio. The MEDD/final methadone dose ratios for those switched for side effects at ≥ 300 mg/day or < 300 mg/day of morphine were 9.1:1 and 5.6:1, respectively, and for those switched for pain at ≥ 300 mg/day or < 300 mg/day of morphine were 4.9:1 and 3:1, respectively. Adequate control of pain and side effects of morphine was achieved by 72.9%.[37]

Another chart review for 189 consecutive outpatients who underwent methadone initiation or rotation confirmed the significant correlation between previous opioid dose and MEDD/methadone dose ratio. Although older age, reason for rotation, and MEDD were significant in the univariate analysis, multivariate analysis revealed only reason for rotation and MEDD before rotation to be significant. The success rate was 92% for initiation and 84% for rotation, while 7% dropped out during the 2 consecutive follow up visits.[38]

In a retrospective chart review of 324 patients, a total of 10 patients with MEDD $>$ 1,200 mg (1,200–10,940 mg daily) revealed no correlation between MEDD and final methadone dose after switching. In all patients in this group, a fixed maximum methadone dose of 30 mg/day produced clinically meaningful improvements in pain scores without adverse drug effects. The authors discussed that beyond the threshold of 1,200 mg/day, cross-tolerance between opioids and methadone appears to become very low.[39]

Issue of switching from transdermal fentanyl

There are limited clinical studies reporting switching from transdermal fentanyl to methadone due to poor pain control or intolerable side effects such as neurotoxicity. In 17 cancer patients, a two-step conversion from transdermal fentanyl to oral morphine using a 1:100 ratio, and then oral morphine to methadone using a 5:1 ratio in general was used; a 10:1 ratio was used for those with fentanyl $>$ 400 μg/h requiring rapid escalation prior to switch or in delirium and presence of questionable history of increasing fentanyl due to pain. Although satisfactory pain management was achieved in 80% of cases, there were no statistically significant correlations between fentanyl dose prior to switching (median 150 μg/h) and final methadone doses on day 7 (median 75 mg /day, with range of 30–135 mg/day). The switch was effective in the somatic pain group but not in the neuropathic pain group.[40] Although no explanation for this phenomenon was discussed, there may be a significant variation of fentanyl absorption, especially at very high doses, as transdermal fentanyl depends on the availability of body fat as a reservoir, and no clear pharmacokinetic data is available at higher doses especially when patients are cachectic.[41] This data supports that clinicians should exercise extreme caution for unnecessary overdose of methadone when initiating a switch directly from fentanyl, especially at higher doses.

Rotation from methadone to other opioid analgesics

To date, there are only few studies reporting on switching from methadone to an alternative opioid.[42–44] The results suggest that conversion factors are not necessarily equivalent when switching the opioid in the opposite direction. Retrospectively reviewed consecutive medical records of 29 patients undergoing a switch from methadone to an alternative opioid due to suboptimal pain control or opioid toxicity revealed a mean dose ratio for oral methadone to oral MEDD of 1:4.7, and a mean dose ratio for intravenous methadone to MEDD of 1:13.5. The mean and median methadone doses prior to switching were 30 mg and 20 mg, respectively, for oral, and 35 mg and 26 mg, respectively, for intravenous. The mean number of days to achieve a stable dose was 2.6 for oral and 2.5 for intravenous methadone.[44] Although the authors attempted to investigate if the dose ratio when switching from methadone to another opioid increased with increasing dose of methadone, analysis did not yield a statistically significant relationship for any of the models used in this study.

Safety in two switching methods: 3-day switch (3DS) vs. stop and go (SAG)

There are two commonly used methods of rotating opioids to methadone. The Edmonton method is a 3-day switching method (3DS) that involves a gradual replacement of the previous opioid with methadone.[6, 44] On the first day, the opioid is reduced by a third and replaced by an equivalent amount of oral methadone in three divided doses. The morphine to methadone ratio used is 10:1 for patients on ≤ 300 mg of morphine and 12:1 for those for higher doses. If the patient continues to complain of pain on the second day, then a further reduction in the original opioid by a third and a corresponding increase in methadone follow. If pain is adequately controlled, then the methadone dose is left unchanged. The switch is completed on the third day, when the original opioid is discontinued and the methadone dose adjusted if indicated. During the first 3 days of switch, the breakthrough analgesic is left as the original opioid; it is then switched to methadone based on the final total daily dose of methadone.

The second method, known as the Morley-Makin or stop and go (SAG) method involves discontinuing all previous opioid and using 10% of the MEDD as the methadone dose, given on as required basis every 3 h.[45] The maximum dose of methadone that can be given is set at 30 mg to prevent potential toxicity. If the patient requires a breakthrough analgesic dose before the allowed 3-hourly methadone doses, then the previous breakthrough opioid dose is used. On day 6, the methadone requirement over the last 2 days is calculated and the patient is switched onto a twice-daily regimen.

A recent randomized trial comparing 21 patients switched using a SAG strategy to 21 patients switched using a 3DS reported that the former had a trend of more pain, serious adverse effects, and drop outs. Two patients died in the SAG group, one from a myocardial infarction and the other from cardiac tamponade and pulmonary embolism. One SAG patient suffered from respiratory depression on day 5. The SAG group received a median methadone dose of 70 (range 30–160) mg/day the first day, whereas the 3DS group received a median dose of 35 (range 5–90) mg/day ($p < 0.001$). The final median methadone doses were 65 (range 30–190) mg/day in the SAG group, and 90 (range 30–240) mg/day in the 3DS group.[46] Based on these findings, the authors concluded that in seriously ill patients requiring large opioid doses, the SAG method should not replace the 3DS. It is important, however, to note that the SAG procedure used in this trial involved replacing the previous opioid with an equianalgesic dose of methadone on day 1 and switching patients over a 6-day period, followed by observation and titration. In the same cohort, the trough serum concentrations of methadone, morphine, morphine-6-glucuronide (M6G), and oxycodone were measured on days 1, 2, 3, 4, 7, and 14. The SAG group was initially more exposed to methadone and less to the replaced opioids but without observed clinical benefit and with a higher dropout rate. The authors suggested that patients switched to methadone should be followed closely for the first 5 days, regardless of switching strategy.[47]

Methadone as breakthrough analgesic

Breakthrough pain is defined as a transitory increase in pain to greater than moderate intensity (i.e. severe or excruciating), which occurs superimposed on controlled baseline pain of moderate intensity of less (i.e. no pain or pain of mild to moderate intensity). It is a highly prevalent phenomenon in cancer pain, and it has been a widely accepted practice to provide a short acting analgesic as needed in addition to the around-the-clock analgesic. It has also been postulated that individuals with chronic pain who use frequent doses of short-acting opioids on a regular basis become physically dependent and develop intermittent withdrawal phenomena including arousal, increased muscular tension and receptor "hunger" between doses of medications. These intermittent withdrawal symptoms may act to increase pain. In cancer patients, end-of-dose failure, i.e. when pain occurs or is markedly worsened at the end of a dosing interval, has been claimed to be a cause for breakthrough pain.[48] Other common etiologies of breakthrough cancer pain are volitional pain, such as bone cancer pain associated with daily activities, and non-volitional pain, such as bowel spasms or neuropathic cancer pain.

The successful administration of oral and sublingual methadone for breakthrough cancer pain has been reported.[49–51]. The interest in sublingually administered methadone for the management of breakthrough cancer pain is based on its lipophilicity, which allows it to be easily absorbed via the sublingual mucosa, high solubility in water, which requires only small volumes for this route of administration, and that fact that it is inexpensive. Sublingual methadone is about 40% bioavailable, and absorption is 80% complete within 10 min, the majority of which is absorbed within the first 2.5 min.[52] Upon absorption, pharmacokinetic/pharmacodynamic modeling has demonstrated that the onset of analgesic action is rapid; once methadone is detectable in the blood, there is an analgesic effect.[53] Although methadone can be administered intravenously, rectally, and subcutaneously, sublingual administration may also be considered with a total volume of 0.5–1.0 ml water under the tongue for full 2 min with maximum concentration of 10 mg/ml of methadone hydrochloride.

Fatal and nonfatal adverse effects

Although limited data has been available in the cancer pain population, the wealth of information from methadone maintenance treatment and chronic non-cancer pain population can help clinicians to learn specific risks associated with methadone and factors that may be associated with overdose. These include the association of methadone use with QT_c interval prolongation and cardiac arrhythmia. The most recently published clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence[54] encourages clinicians to obtain an electrocardiogram (ECG) prior to

initiation of methadone in patients with risk factors for QT_c interval prolongation, any prior ECG demonstrating a $QT_c > 450$ ms, or a history suggestive of prior ventricular arrhythmia (such as macrolides antibiotics, quetiapine, tricyclic antidepressants, and cocaine).[54] Although no study has evaluated the effect of ECG screening and monitoring on clinical outcomes, and the clinical opinion on the need to obtain ECGs in patients being considered for methadone varies markedly, in part because of concerns about delayed or reduced access to methadone, an ECG is the only way to detect asymptomatic QT_c interval prolongation. Patients with QT_c interval prolongation might benefit from efforts to address causes of QT_c interval prolongation, consideration of alternative opioids or other interventions, or additional monitoring if prescribed methadone. Clinicians are encouraged to screen for cardiac risk factors, such as prolonged QT_c interval, known cardiac arrhythmias, a recent myocardial infarction, or a family history of early cardiac death.

A literature review indicated that the prevalence of addiction to opioids varies from 0% up to 50% in chronic noncancer pain patients, and 0% to 7.7% in cancer patients, depending on the population studied and the criteria used.[55] A recent population-based study revealed that the use of benzodiazepines was strongly associated with chronic opioid use for chronic pain management. The chronic use of opioid was also strongly associated with smoking, use of cannabis, and alcohol abstinence with a history of significant alcohol use. Benzodiazepines have been shown to increase the subjective rating of "strength of drug effect," "drug liking," and "good effects" of opioids, and this may partly explain the high prevalence of benzodiazepine use among long-term opioid users.[56] Medications prescribed for psychiatric problems (such as fluoxetine, amitriptyline, quetiapine, and alprazolam) also can increase methadone accumulation and risk of toxicity. Other risk factors can be patients with a respiratory disorder, cor-pulmonale, morbid obesity, sleep apnea syndrome, myxedema, or kyphoscoliosis, or central nervous system depression.[54] In such patients, even customary therapeutic doses of methadone can suppress respiratory drive while simultaneously increasing airway resistance to the point of apnea. In such patients, methadone should be used at the lowest effective dose and only under careful medical supervision.[57]

DISCUSSION

Factors influencing the conversion dose ratio to methadone

The equianalgesic dose ratio for methadone is difficult to predict especially when previous opioid analgesics were at very high dose. This can add further complexities in switching to methadone on top of a wide range of parameters of pharmacokinetics, the potential for drug-drug interactions with concurrent pharmacotherapies as well as the potential risk for fatal side effects. A consistent finding has been reported that the higher the MEDD, the wider the variation and unpredictability of the final dose of methadone after switching.[36, 37, 39] This observation may not be fully explained by cross-tolerance or distinctive differences between previous opioids and methadone at the level of receptor interactions only, while another possibility is that dose reduction resulted in improvement of opioid-induced hyperalgesia (OIH).

Hyperalgesia, tolerance, and potential negative consequence of long-term opioid administration

μ-Opioid receptor agonists have been known to provide analgesic effects by raising the pain threshold and alleviating anxiety, through receptor coupling to μ-opioid receptors, which induces hyperpolarization and causes presynaptic inhibition, subsequently depressing release of neurotransmitters such as glutamate, acetylcholine, norepinephrine, serotonin, and substance P. However chronic therapy with μ-opioid receptor agonists could paradoxically induce or sensitize patients to severe pain, a condition termed opioid-induced hyperalgesia (OIH). This phenomenon is characterized by a heightened perception of pain related to the use of opioids, in the absence of disease progression or opioid withdrawal. Accumulating evidence suggests that the administration of opioid analgesics leads not only to analgesia but may also lead to a paradoxical sensitization to noxious stimuli.[58]

OIH is generally thought to result from neuroplastic changes in the peripheral and central nervous system that lead to sensitization of pronociceptive pathways. However, research efforts have struggled to develop a consensus definition of OIH and incorporate this into experimental protocols designed to identify this effect. In cancer pain management particularly, disease progression or opioid analgesic tolerance are considered as reasons to escalate opioid analgesics, without clearly defined criteria. In this assumption, pain may respond appropriately to increased dose of opioid analgesics; however, manifestations of OIH may intensify with higher opioid dosing.[58]

Abnormal neuron excitability results mainly from central sensitization, a complex sequence of events that show a strong dependence on NMDA-receptor activation and are blocked by specific antagonists. NMDA receptors, which are located presynaptically on central terminals of primary afferent neurons as well as postsynaptically on dorsal horn neurons, are known to play an important role in OIH and tolerance.[59, 60] Although there has not been further clinical evidence to confirm the role and effectiveness of methadone as an NMDA antagonist in the cancer pain population, the preventative effect on μ-opioid receptor tolerance, antihyperalgesic effects, and antinociceptive effects on neuropathic pain may partially explain the significantly high conversion ratio of morphine or other opioid analgesics to methadone, especially at very high doses. Together with the unique property of methadone in μ-receptor endocytosis and re-sensitization,[61] methadone may play an especially significant role in patients who do not achieve desirable analgesia even with very high doses of opioid prior to

switching to methadone.

Cancer pain as a complex biopsychosocial experience

Another possible contributor to the widely variable equianalgesic dose ratio to methadone is potentially inappropriate use of the opioid analgesics in pain syndromes that are not responsive to opioid analgesics. Pain in general and especially cancer pain is a biopsychosocial experience with a significant cognitive and emotional component. In advanced cancer, the incidence of anxiety is 13% to 79%, while depression is seen in 3% to 77% of the patients.[62, 63] Cancer patients with anxiety and depression express higher levels of pain.[62] This would imply inappropriate use of opioids for the "pain experience" and suffering.[64] Major depressive disorder and serious psychological distress have been identified as significant factors associated with the higher incidence of drug abuse,[65] which suggests that affected patients may demand higher doses of analgesics. Although searches for genetic or disease-specific modulators of this have so far proven unsuccessful,[66] data from our group has also suggested that significant psychological distress, addiction, and neuropathic pain are statistically significantly associated with higher opioid analgesic requirements.[67]

Furthermore, an international multicenter study to identify the key variables relevant for cancer pain treatment outcome revealed that the presence of breakthrough pain and psychological distress were significant contributing factors, together with sleep disturbances and opioid dose.[68]

Although there is a still room for discussion regarding this practice, it is possible that some patients are on higher doses of opioid analgesics because they have developed tolerance and hyperalgesia, and therefore require relatively lower doses of methadone due to only small fraction of cross-tolerance between previous opioids and methadone for analgesia as well as adverse effects.

Non-analgesic effects of μ-opioid receptor agonists are also significant. For short-term use, sedation, reducing response to CO_2, and stimulating the chemoemetic trigger zone in the dorsal brainstem, especially in the ambulatory population, are commonly observed. Effects of both short- and long-term use may include increasing intestinal resting tone, decreasing biliary and pancreatic and intestinal secretions, inhibition of GABA therefore stimulating rewarding properties, stimulating parasympathetic nervous system, reducing hypothalamic-pituitary hormones such as gonadotropin releasing hormone and corticotrophin releasing hormone,[69] and finally increasing chance of infection through immunosuppression.[70]

Preclinical models have also shown that prolonged exposures to morphine is associated with increased osteoclast activity and upregulated interleukins (IL-1β), accelerated sarcoma-induced bone destruction and double the incidence of spontaneous fracture, in a dose- and naloxone-sensitive manner.[71] Furthermore, clinical studies in chronic nonmalignant pain have provided evidence for opioid-induced androgen deficiency in men and profound inhibition of ovarian sex hormone and adrenal androgen production in women (i.e. opioid-associated hypogonadotrophic hypogonadism) who chronically consume opioids, which may affect bone health.[72–74] Bone mineral density was found to be lower in patients on methadone maintenance therapy than in normal control subjects.[74] In addition, recent preclinical studies revealed that morphine at clinically relevant doses stimulates angiogenesis and promotes tumor growth in mice.[75–77] A recent clinical study also supported that higher μ-opioid receptor expression in prostate tumor cells and opioid analgesic requirements are associated with shorter progression-free survival and overall survival in patients with metastatic prostate cancer.[78]

Potential of methadone as co-analgesic to prevent opioid-induced hyperalgesia

The standard of practice in cancer pain management involves the liberal use of around-the-clock opioids with frequent breakthrough doses of short-acting opioid as often as every 1–2 h. This way, the opioid dose may be rapidly titrated upward without a ceiling dose. However, this long-believed standard approach of opioid dose escalation may have paradoxically caused a decrease in analgesic effect while requiring much higher doses. Earlier studies focused on the toxic effects of opioid metabolites, such as morphine-3-glucuronide, and hydromorphone-3-glucuronide, which were shown to have neurotoxic activities in animal models. However, OIH has been demonstrated with drugs not limited to the phenanthrene class (morphine, hydromorphone, oxycodone etc.) or methadone, but including synthetic classes of drugs such as phenylpiperadines (fentanyl, meperidine etc.).

Based on the realization of potential negative consequence of opioid dose escalation, a recent case series of 93 patients suggested a potential role for low-dose methadone as a long-acting agent combined with short-acting morphine as needed or other opioid analgesics around the clock. Methadone as a co-analgesic may harness the potential benefits of NMDA-receptor antagonism, without the risks associated with reaching high methadone doses during a switch from other opioids, particularly in an environment that lacks expertise such as acute medical wards.[79, 80] Also, combining opioids with low-dose methadone may have potential pharmacodynamic interactions through modulating receptor endocytosis and re-sensitizing μ-opioid receptor dimers bound to morphine or other μ-opioid agonists. Therefore, the therapeutic index may improve, while reducing the dose requirement. This may diminish the risk of developing analgesic tolerance, while preventing life threatening side effects of methadone especially at high dose. However, there are number of unknowns, such as potential synergic adverse effects, presence of a certain pain phenotype for which opioid combination would be advantageous, and therapeutic dose range to produce antinociceptive synergy.

CONCLUSION

Taken together, strategies to approach cancer pain have been slowly but steadily progressing, though not at the speed of cancer treatment strategies so far. The early involvement of palliative care in cancer trajectories and the longer life span of people with cancer have been providing a new understanding of the importance of assessment of cancer pain, as well as recognition of the downsides of chronic opioid analgesic therapy. This concern is further supported by the clinical experience and research in long-term opioid therapy for chronic non-cancer pain, which were initially influenced by cancer pain management, and are now providing significant insight for the limitation and potential of methadone.

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